

Specification

1. Title of invention: **FOAM AEROSOL PREPARATION**

2. Claims

1) A foam aerosol preparation, comprising an active ingredient of an acidic non-steroidal anti-inflammatory analgesic compound.

2) A foam aerosol preparation, comprising:

0.2-5 % by weight of an acidic non-steroidal anti-inflammatory analgesic compound;

1-20 % by weight of an absorption promoting agent;

0.3-10 % by weight of a surface active agent;

0.01-5 % by weight of a pH-adjusting agent;

10-50 % by weight of purified water;

10-50 % by weight of a propellant.

3) A foam aerosol preparation as described in Claim 1 or Claim 2, wherein said acidic non-steroidal anti-inflammatory analgesic compound is selected from a group consisting of ibuprofen, indomethacin, ketoprofen, flurbiprofen, naproxen,

pranoprofen, suprofen, felbinac, diclofenac, piroprofen, sulindac, miroprofen, tiaprofen, protidinic acid, fenbufen, loxoprofen, ketorolac, bermoprofen, nabumetone, and their derivatives.

4) A foam aerosol preparation as described in Claim 2, wherein said absorption promoting agent is selected from a group consisting of crotamitone, benzyl alcohol, glycol salicylate, peppermint oil, an alcohol ester of a monocarboxylic acid with a carbon number of C<sub>4</sub>-C<sub>15</sub>, and liquid higher alcohol.

### 3. Detailed description of the invention

#### (1) Field of use in the industry

The present invention relates to a foam aerosol preparation containing an acid non-steroidal anti-inflammatory analgesic compound as the active ingredient. Described in further detail, the present invention relates to a foam aerosol preparation having an acidic non-steroidal anti-inflammatory analgesic compound as the active ingredient, and it is effective as a treatment for orthopedic ailments such as muscle pain, back pain, joint pain, and the like.

## **(2) Prior art**

For aerosol preparations containing acid anti-inflammatory analgesic compounds of the prior art, an aerosol preparation containing indomethacin is known from Japanese Laid-Open Patent Publication Number 61-83117. In this preparation, indomethacin is mixed in a known aerosol preparation. In addition, in Japanese Laid-Open Patent Publication Number 61-266428, the present inventors proposed an aerosol preparation containing a non-steroidal anti-inflammatory analgesic compound. This is a cracking type of foam aerosol preparation and is a completely different invention from the foam aerosol preparation of the present invention.

## **(3) Problems to be solved by the invention**

In general, acidic anti-inflammatory analgesic compounds have a strong anti-inflammatory action without any serious side-effects. As a result, in the field of orthopedics, they have been used in many forms including oral forms and external forms and the like. However, when made into an aerosol preparation, because acidic anti-inflammatory analgesic compounds irritate the nasal mucous membrane, it can result in sneezing, or in extreme cases, it can cause asthma attacks. Therefore, the object of the present invention is to manufacture an anti-inflammatory analgesic compound aerosol preparation which does not irritate the nasal mucous membrane.

**(4) Means for solving the problems**

Upon considering the current situation, the present inventors have conducted intensive research, and as a result, it was discovered that by combining an acidic anti-inflammatory analgesic compound into a foam aerosol preparation the above problems were solved. In other words, the present invention relates to an external anti-inflammatory analgesic foam aerosol preparation, wherein: a solution of an acidic anti-inflammatory analgesic compound, a surface active agent, an absorption promoting agent, and purified water is combined with a propellant.

The present invention is described in further detail below.

Examples of acidic anti-inflammatory analgesic compounds that are used in the present invention include ibuprofen, indomethacin, ketoprofen, flurbiprofen, naproxen, pranoprofen, suprofen, felbinac, diclofenac, piroprofen, sulindac, miroprofen, tiaprofen, protidinic acid, fenbufen, loxoprofen, ketorolac, bermoprofen, nabumetone, and their ester derivatives and the like. Depending on the effective amount for each, these are mixed in the range of 0.2-5 % by weight, and preferably mixed at 0.3-4 % by weight. Furthermore, in addition to these active ingredients, local stimulants, such as menthol, camphor, peppermint oil, nonyl vanillyl amide, capsaicin and the like, can be combined as an auxiliary agent.

Examples of the absorption promoting agent include chrotamiton; benzyl alcohol; glycol salicylate; peppermint oil; alcohol esters of monocarboxylic acid with a carbon number of C<sub>4</sub>-C<sub>15</sub> such as diisopropyl adipate, diethyl sebacate, diisopropyl sebacate, isopropyl myristate, isopropyl palmitate; and liquid higher alcohols such as oleyl alcohol, 2-octyl dodecanol, 2-hexyl decanol, and the like. These absorption promoting agents are combined at 1-20 % by weight, preferably 2-10 % by weight, and are of one type or a combination of two or more types. For the surface active agent, although either ionic or non-ionic may be used, non-ionic surface active agents are preferred. Examples of surface active agents include sorbitan fatty acid ester, glycerine fatty acid ester, polyglycerine fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene sorbitol fatty acid ester, polyoxyethylene glycol fatty acid ester, polyoxyethylene hardened castor oil, polyoxyethylene alkyl ether, polyoxyethylene polyoxypropylene alkyl ether, polyoxyethylene phenyl ether, higher alcohol phosphate, and the like. These surface active agents can be used singly or two or more types can be combined. They are mixed at 0.3-10 % by weight, preferably 0.5-5 % by weight, and even more preferably 1-4 % by weight. Furthermore, in order to aid in the emulsification of these surface active agents, an emulsification aiding agent can be added. Examples of emulsification aiding agents include higher alcohols such as cetanol, stearyl alcohol, cetostearyl alcohol, cholesterol, behenyl alcohol, and the like,

and lecithin, saponin and the like. For the pH adjusting agent, there are inorganic bases such as potassium hydroxide, sodium hydroxide, ammonia water and the like, and organic bases such as diethanol amine, diisopropanol amine, triisopropanol amine, triethanol amine, and the like. These pH adjusting agents are combined at 0.01-5 % by weight in an amount that results in a pH for the preparation of 4-9, and preferably a pH of 5-8. Furthermore, a preservative is mixed as needed. For the preservative, common preservatives, including parabenes, such as methyl parabene, ethyl parabene, propyl parabene, and the like, and phenols such as isopropyl methyl phenol, thymol, and the like are mixed in appropriate amounts.

In addition, other additives for improving the feel of the product, such as powders such as talc, silicon powder, nylon powder, and the like, wetting agents such as propylene glycol, 1,3-butylene glycol, 3-methyl-1,3-butane diol, and the like, and ethanol, isopropanol, and the like can also be mixed. For the propellant, propellants commonly used in aerosol preparations such as liquefied natural gas, n-pentane, isopentane, Freon gas such as Freon 11, Freon 12, Freon 142b, Freon 123, Freon 134a, Freon 124, Freon 132b, Freon 133a and the like, dimethyl ether, carbon dioxide gas, and the like are used. The mixing amount of these propellants is in the range of 10-50 % by weight, and the amount added is such that the pressure of the preparation is 1-8 kg/cm<sup>2</sup>.

Next, the manufacturing method for the foaming aerosol preparation of the present invention is described.

In order to manufacture the aerosol preparation of the present invention, first, an absorption promoting agent is added to the active ingredient and is dissolved or dispersed. After adding the surface active agent, pH adjusting agent, purified water, and other additives, a valve is attached, and this is sealed, and the propellant is forced inside. The above manufacturing method is only one example, and manufacture is possible even when the sequence of manufacturing steps is altered.

The embodiments are shown below, and they will describe the present invention in more concrete terms.

*Embodiment 1*

2g of ketoprofen was added to 3g of chrotamiton and was heated to 70 degrees and dissolved. 1g of 1,3-butylene glycol, 1g of cholesterol, 2g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 0.1 g of diisopropanol amine, and 60 g of water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 2*

1g of ketoprofen was added to 5g of diethyl sebacate and 0.5 g of peppermint oil and was heated to 70 degrees and dissolved. 2g of 1,3-butylene glycol, 1g of cetostearyl alcohol, 1g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 0.1 g of triethanol amine, and 60 g of water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 3*

2g of ketoprofen and 2g of l-menthol were added to 5g of diisopropyl adipate and 0.5g of peppermint oil and were heated to 70 degrees and dissolved. 2g of 1,3-butylene glycol, 1g of cholesterol, 1g of talc, 1g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 0.2g of diisopropanol amine, and 60 g of purified water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.



*Embodiment 4*

2g of felbinac and 2g of l-menthol were added to 2g of chrotamiton and was heated to 70 degrees and dissolved. 2g of propylene glycol, 1g of cholesterol, 1g of talc, 5g of ethanol, 1g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 1.0g of diisopropanol amine, and 60 g of purified water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 5*

2g of ketoprophen was added to 2g of chrotamiton and was heated to 70 degrees and dissolved. 2g of propylene glycol, 1g of cholesterol, 2g of squalane, 1g of talc, 2g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 0.2 g of diisopropanol amine, 0.1g of methyl parabene and 60 g of purified water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas/dimethyl ether (70/30 wt %) was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 6*

1g of ketoprofen was added to 2g of oleyl alcohol and 5g of diethyl sebacate and was heated to 70 degrees and dissolved. 2g of propylene glycol, 1g of cholesterol, 0.1% of carboxyvinyl polymer, 1g of talc, 5g of ethanol, 1g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 1g of polyoxyethylene (23) cetyl ether, 0.2 g of diisopropanol amine, and 60 g of purified water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 7*

2g of ketoprofen was added to 2g of chrotamiton and was heated to 70 degrees and dissolved. 2g of propylene glycol, 1g of cholesterol, 0.1% carboxyvinyl polymer, 1g of talc, 5g of ethanol, 1g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 1g of monododecyl phosphate, 1.2 g of diisopropanol amine, and 60 g of water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 8*

1g of indomethacin was added to 3g of chrotamiton and was heated to 70 degrees and dissolved. 2g of 1,3-butylene glycol, 1g of cholesterol, 1g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 0.08 g of triethanol amine, and 60 g of water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 9*

1g of loxoprophen was added to 3g of chrotamiton and was heated to 70 degrees and dissolved. 2g of 1,3-butylene glycol, 1g of cholesterol, 1g of polyoxyethylene (20) polyoxypropylene (8) cetyl ether, 0.08 g of triethanol amine, and 60 g of purified water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 17.6 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Embodiment 10*

2g of ketoprophen was added to 1g of chrotamiton and was heated to 70 degrees and dissolved. 2g of 1,3-butylene glycol, 2g of oleyl alcohol, 0.1g of cholesterol, 3g of

polyoxyethylene (10) octyl phenyl ether, and 49.9 g of purified water were added and emulsified. This was placed in a pressure container. After attaching a valve and sealing, 23.2 g of liquefied petroleum gas was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Reference example 1*

0.75g of indomethacin was dissolved in a mixture solution of 3g of diisopropyl adipate, 5g of polyethylene glycol monolaurate, 10g of ethanol, 10g of isopropanol, and 5g of macrogol 400. Next, 0.1g of dibutyl hydroxy toluene was added and dissolved. Next, 23g of purified water in which 0.2g of diisopropanol amine was dissolved was added and mixed. This was then placed in a pressure container. After attaching a valve and sealing, 10g of liquefied petroleum gas and 15g of dimethyl ether was forced inside, resulting in an anti-inflammatory analgesic foaming aerosol preparation.

*Test 1*

With regard to the aerosol preparations in Embodiment 1 and Reference example 1, the degree of irritation to the nasal mucous membrane was studied.

Twenty healthy adult males were sprayed on the upper arm with the aerosol preparations of Embodiment 1 and Reference example 1, and the irritation to their nasal mucous membranes were studied. Referring to Table 1, the results are shown.

**Table 1.** Mucous membrane irritation test of the aerosol preparations

	Number of people who reported irritation to the mucous membrane
Aerosol preparation of Embodiment 1	None
Aerosol preparation of Reference example 1	15

As is clear from Table 1, compared to the aerosol preparation of the reference example, the aerosol preparation of the present invention did not have dispersal of its contents. As a result, there was no irritation to the nasal mucous membrane.

#### **(5) Advantages of the invention**

With the foam aerosol preparation of the present invention containing an acidic anti-inflammatory analgesic compound as the active ingredient, when sprayed, the bubbles are small and do not burst. As a result, there is no irritation to the nasal

Translated by Yukiko Otsuka Lee  
September 18, 2002

**Japanese Laid-Open Patent Publication No. 3-72433**

Laid-Open Date: 3/27/1991

mucous membrane by the active ingredients. The aerosol preparation of the present invention is superior because of its high degree of safety. In addition, because an absorption promoting agent is mixed in, there is good absorption through the skin, and the present invention is superior in terms of drug effectiveness. Furthermore, there is no stickiness, and because the bubbles break rapidly, it feels nice. The present invention is suitable as a preparation in the orthopedic field.

As described above, the foam aerosol preparation of the present invention is valuable as a treatment for inflammatory ailments such as muscle pain, back pain, joint pain, bruising, spraining, inflammation of the tendon and the like.